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Case Report

Inappropriate Secretion of Antidiuretic Hormone after Pancreatoduodenectomy for Pancreatic Head Cancer: A Case Report and Literature Review

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Keywords
SIADH · Pancreaticoduodenectomy · Post-operation

Abstract
Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a disease that leads to dilute hyponatremia through excessive secretion of antidiuretic hormone. SIADH has various causes, including ectopic ADH-producing tumors, drug properties, and can be idiopathic. But there have been very few reports of cases in which SIADH has developed after surgery for malignant tumors. In addition, few cases have been reported where this disease has developed after surgery for pancreatic cancer, because the symptoms of hyponatremia are nonspecific. These symptoms are particularly gastrointestinal symptoms; therefore, it is difficult to differentiate them, even if SIADH has developed after gastrointestinal surgery. The patient in our case was an 80-year-old woman. She had persistent epigastralgia and left back pain. Imaging studies revealed a tumor in the head of the pancreas, which was diagnosed as pancreatic head cancer. We performed subtotal stomach-preserving pancreatoduodenectomy. After the operation, she complained of appetite loss and general fatigue. Her serum sodium levels decreased to 109 mEq/L on postoperative day 11. She was diagnosed with SIADH using the SIADH diagnostic criteria listed by the Japanese Ministry of Health, Labor and Welfare. We treated the patient with sodium supplementation for hyponatremia, and her symptoms ameliorated. After the event, she did not relapse with hyponatremia. This case is significant in that we performed differential diagnosis after major gastrointestinal surgery for pancreatic cancer and diagnosed SIADH at an early stage.

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Introduction

Hyponatremia, defined as an excess of water in relation to sodium in the extracellular fluid, is the most common electrolyte disorder in hospitalized patients. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is one of the most frequent causes of hyponatremia [1]. SIADH is a condition defined as the unsuppressed release of antidiuretic hormone (ADH) from the pituitary gland or nonpituitary sources or the continued action of vasopressin receptors [2]. It has several causes, including ectopic ADH-producing tumors, drugs, surgery, and idiopathic. However, it is relatively rare for SIADH to be developed after major gastrointestinal surgery for cancer. Symptoms of hyponatremia include nausea, decreased appetite, and poor general condition; therefore, it is difficult to determine a specific diagnosis for such symptoms after gastrointestinal surgery.

We report this case of SIADH after pancreatoduodenectomy for pancreatic cancer that was diagnosed relatively early and treated with sodium supplementation.

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The patient was an 80-year-old woman who had no family history of cancer. She complained of upper abdominal pain. Contrast-enhanced computed tomography showed a mass at the head of the pancreas (Fig. 1a). Endoscopic ultrasonography showed that the main pancreatic duct in the head of the pancreas was disrupted, and a 17 × 10 mm hypoechoic mass was observed. Magnetic resonance cholangiopancreatography demonstrated that the diameter of the main pancreatic duct extended irregularly into the tail of the pancreas (Fig. 1b). Obstruction of the main pancreatic duct at the head of the pancreas was observed. Cytology of the pancreatic juice and pancreatic duct suggested ductal carcinoma. Laboratory examinations did not reveal any remarkable abnormalities: the patient's carcinoembryonic

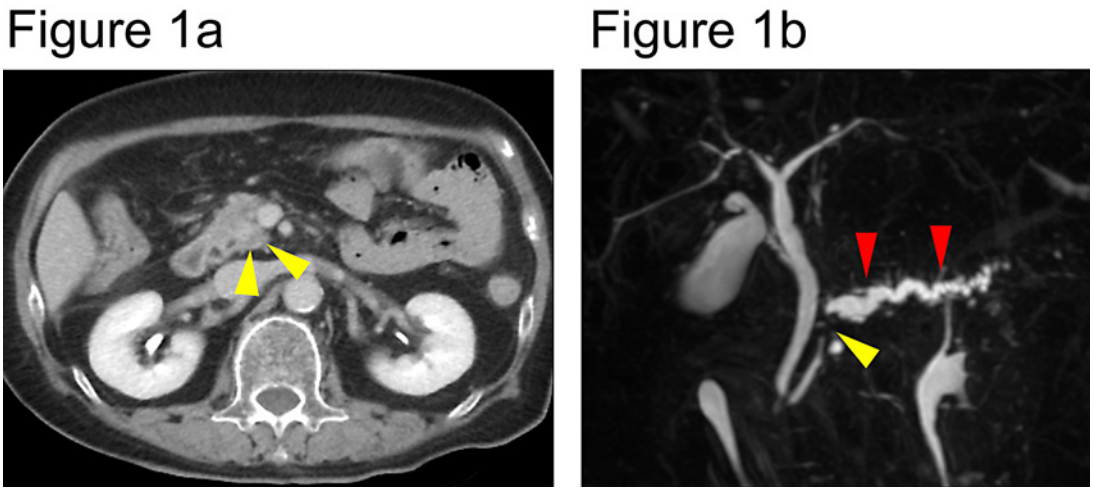

Fig. 1. Preoperative imaging examination revealed pancreatic head cancer. **a** Contrast-enhanced computed tomography showed a tumor in the head of the pancreas (yellow arrowheads). No significant lymphadenopathy was observed. Liver, bone, and lung metastases were not detected. **b** Magnetic resonance cholangiopancreatography showed that the diameter of the main pancreatic duct extended irregularly in the tail of the pancreas (red arrowheads). Obstruction or disruption of the main pancreatic duct was observed over 10 mm on the cranial side of the pancreatic head (yellow arrowhead).

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Figure 2a

Figure 2b

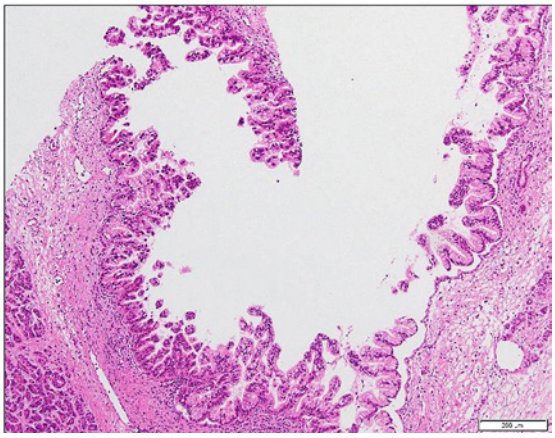

Fig. 2.a The mass extended beyond the pancreatic capsule and the surrounding lymph nodes were also slightly enlarged. An extension of the intraductal duct was noted at the stump of the pancreas, and a total of three additional resections were performed. **b** Histological examination of a resected pancreas specimen revealed moderately differentiated invasive ductal carcinoma. The clinical stage was categorized as pT3 N1 cM0 G2 Stage IIB, pCH0, pDU0, pS0, pRP1, pPV0, pA0, pPL0, pOO0 in accordance with the Union for International Cancer Control tumor node metastasis classification for pancreatic cancer 8th edition.

antigen level was 1.5 ng/mL (normal range, <5.0 ng/mL), carbohydrate antigen 19-9 level was 5 U/mL (normal range, <37 U/mL), cancer antigen 125 level was 9 U/mL (normal range, <35 U/mL), SPan-1 level was <10 U/mL (normal range, <30 U/mL), and DUPAN-2 level was <25 U/mL (normal range, <150 U/mL). The electrolyte values were Na 139 mEq/L, K 4.2 mEq/L, and Cl 109 mEq/L, all of which were within normal limits.

Subtotal stomach-preserving pancreatoduodenectomy, D2 lymph node dissection, and type II reconstruction were performed. We diagnosed the patient with moderately differentiated pancreatic invasive ductal carcinoma, pathological T3 N1 M0 G2 Stage IIB, in accordance with the Union for International Cancer Control tumor node metastasis classification for pancreatic cancer 8th edition (Fig. 2a, b).

The patient progressed without major abnormal findings for about a week after surgery. The patient complained of appetite loss and general fatigue on postoperative day (POD) 7, and the serum sodium level was 129 mEq/L at this time. At first, we considered this situation as delayed gastric emptying (DGE), but she did not have any vomiting, and the drainage volume of gastric tube had not increase after surgery. So that we thought it unlikely that these factors were responsible for the hyponatremia. Her symptoms gradually worsened, and her serum sodium level decreased to 109 mEq/L on POD 11. She was diagnosed with hyponatremia. SIADH, adrenal insufficiency, and hypothyroidism were all considered to have caused this stage. Additional tests revealed an increased level of ADH (5.7 pg/mL, normal range <2 pg/mL), decreased level of plasma osmolality (224 mOsm/kg, normal range, 275–290 mOsm/kg), increased level of urine osmolality (453 mOsm/kg, normal range, 50–1,300 mOsm/kg), although the level of plasma osmolality was low. Urinary sodium level was also relatively high (72.8 mEq/L, normal range, 40–90 mEq/L). Serum cortisol level (14.6 μg/dL, normal range, >6 μg/dL) and adrenocorticotropic hormone (ACTH) level (21.9 pg/dL, normal range, 7.0–56.0 pg/dL) were not elevated (Table 1). Serum levels of TSH, FT3, FT4, ACTH were also within the normal range; and steroids had not been prescribed before surgery. Therefore, the

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Table 1. The patient's laboratory data showed when the patient develops hyponatremia

Main symptoms	Matching	
Dehydration	–	
Symptoms of hyponatremia	+	
Essential item	Matching value	Laboratory data
P-sodium (Na), mEq/L	<135	109
ADH, pg/mL	More than measurement	5.7
P-osmolality, mOsm/kg	<280	224
U-osmolality, mOsm/kg	>300	453
U-sodium (Na), mEq/L	<20	72.8
Creatinine (Cr), mg/dL	<1.2	0.34
P-cortisol, μg/dL	>6	14.6
Reference item	Matching value	Laboratory data
P-renin activity, ng/mL/h	<5	1.4
P-uric acid, mg/dL	<5	–

Limiting water intake improves hyponatremia without progressive dehydration. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) diagnostic criteria were published by the Japanese Ministry of Health, Labor and Welfare in 2011

diagnoses of adrenal insufficiency and hypothyroidism were ruled out [3, 4]. The possibility of SIADH was also considered based on the results of other tests. She met the SIADH diagnostic criteria listed by the Japanese Ministry of Health, Labor and Welfare (Table 1), due to which we diagnosed the patient with SIADH.

The patient was administered sodium (600 mEq/day) intravenously for 4 days; the dose was gradually tapered as she recovered. We also administered hydrocortisone 10 mg/day for 3 days. The patient developed cholangitis on POD 17, which was treated with sulbactam/cefoperazone. Her serum sodium levels were normal and remained stable (Fig. 3). She was discharged on POD 42 in good condition. After discharge, no symptoms due to hyponatremia were observed.

Discussion/Conclusion

Hyponatremia is one of the most common electrolyte abnormalities, and SIADH is one of the most common causes of hyponatremia [1]. SIADH is characterized by hyponatremia due to excessive secretion of ADH and fluid retention; many kinds of surgical stress increase ADH secretion [2]. Increase in inflammatory cytokines, decrease in circulating plasma volume, drugs, loss of extracellular fluid, cerebral damage due to anesthesia, dysfunction of organs, and surgical pain can lead to the development of hyponatremia after surgery. Moreover, the body's ability to maintain homeostasis declines with age. These factors may increase the likelihood of elderly patients developing SIADH in the postoperative period. Our patient was an 80-year-old woman who was administered general anesthesia and underwent invasive surgery; this may have caused her to be susceptible to postoperative SIADH.

We searched for "SIADH, pancreatoduodenectomy," "SIADH, post operation," "SIADH, cardiac surgery," and "SIADH, abdominal surgery" in PubMed, and identified 10 cases reported

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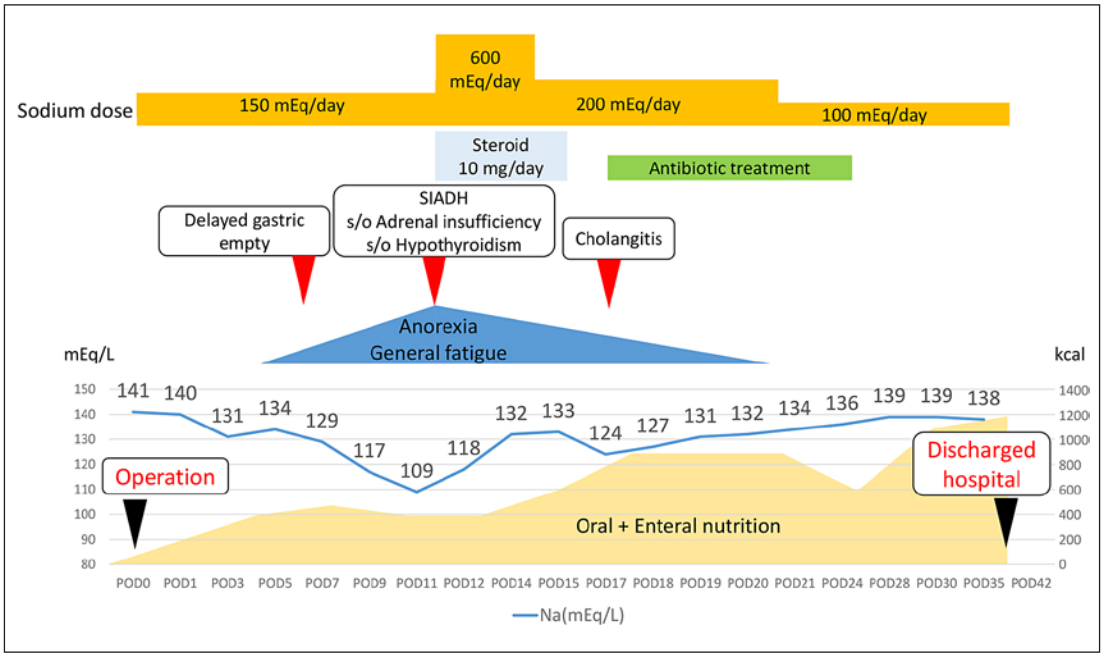

Fig. 3. We initiated treatment for syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Sodium supplementation effectively treated the hyponatremia and improved the patient's symptoms. The figure shows the patient's progress during hospitalization.

Table 2. We searched for cases of postsurgical syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in PubMed using the search terms "SIADH, pancreatoduodenectomy," "SIADH, post operation," "SIADH, cardiac surgery" and "SIADH, abdominal surgery," and this table shows 11 cases of postsurgical SIADH including our case

First author [Ref.]	Year of publishing	Age, years	Underlying disease	Operation	Onset, POD	Na, mEq/L
Ting [5]	1980	5	Atrial septal defect	Heart surgery	–	–
Cornforth [6]	1998	71	Gallstones	Laparoscopic cholecystectomy	3	112
Weber [7]	2003	–	Inguinal hernia	Laparoscopic inguinal hernia repair	–	–
Ruan [8]	2009	68	Choledocholithiasis	Common bile duct exploration and stone removal	1	–
Ahmed [9]	2012	74	Inguinal hernia	Laparoscopic inguinal hernia repair	4 h	116
Iwase [10]	2013	68	Duodenal cancer	Pancreaticoduodenectomy	11	117
Kawaguchi [11]	2013	45	Acute lymphoblastic leukemia	Unrelated bone marrow transplantation	21	–
Boursiquot [12]	2016	76	Esophageal adenocarcinoma	Minimally invasive esophagectomy	–	123
Takagi [13]	2017	15	Biliary atresia	Liver transplantation	34	109
Iqbal [14]	2018	12	Immature ovarian teratoma	Right salpingo-oophorectomy, omentectomy, and peritoneal stripping	–	123
This case	**2019**	**80**	**Pancreatic head cancer**	**Pancreatoduodenectomy**	**11**	**109**

in 10 articles (Table 2) [5–14]. Notably, only 1 of the 10 patients had undergone pancreatoduodenectomy. Iwase et al. [10] reported a case of SIADH caused by administering selective serotonin reuptake inhibitors after pancreatoduodenectomy for carcinoma of the ampulla of Vater. The majority of patients diagnosed with SIADH have a reduced circulating blood

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volume, and treatment with fluid restriction may lead to the development of cerebrovascular disease and consequent worsening of their neurological status. Hypotonic fluid infusion has also been reported as an iatrogenic cause of hyponatremia [15]. It is known that SIADH is more likely to develop in patients with intracranial disease and lung cancer as well as in elderly patients. However, Table 2 shows that postoperative SIADH development was confirmed after surgeries with varying degrees of invasiveness, from hernia repair to liver transplantation. Furthermore, the age and sex of patients with SIADH varied. However, we believe that several cases of postoperative hyponatremia are not correctly diagnosed as occurring due to SIADH, and are not treated correctly. We therefore believe that further case accumulation is necessary.

The symptoms of SIADH are dependent on the degree of hyponatremia and the rate at which the condition progresses. If the patient's serum sodium levels are around 120 mEq/L, only nausea and anorexia appear. However, when serum sodium levels decrease to less than 110 mEq/L, serious symptoms such as impaired consciousness and cramps occur; the condition can turn fatal at this point [2]. In our case, the serum sodium level fell to 109 mEq/L. Fortunately, there were no severe symptoms such as unconsciousness, and only mild symptoms such as nausea and anorexia were observed. Although the symptoms were non-specific, it is unlikely that the hyponatremia was caused by vomiting or DGE in this case, and we conducted a thorough investigation. Some criteria are available for diagnosing SIADH; for example, the diagnosis criteria of SIADH listed by the Japanese Ministry of Health, Labor and Welfare and the Schwartz and Bartter Clinical Criterion (1967), which are regularly updated [2]. In this case, the diagnosis was made using the Japanese diagnostic criteria (Table 1).

Adrenal insufficiency and hypothyroidism can also cause hyponatremia. The rapid ACTH test is normally used to diagnose adrenal insufficiency. However, in our case, no apparent deviation of ACTH and cortisol was observed on blood sampling. Therefore, adrenal insufficiency was not considered to have developed and the rapid ACTH test was not used [3]. TSH levels were also within the normal range, leading us to exclude the possibility of hypothyroidism [4]. Based on the above findings, exclusion diagnosis was also performed, and all items of the diagnostic criteria for SIADH were satisfied; therefore, the patient was diagnosed with SIADH.

In general, the treatment of SIADH is sodium supplementation. Water intake should be limited to 15–20 mL/kg body weight, and administration of over 200 mEq sodium should also be considered. If the patient is in a critical condition, diuretic drugs should be administered intravenously at 10–20 mg as needed and 3% saline equivalent to the amount of sodium excreted in urine should be administered [1]. In our case, the lowest serum sodium level was 109 mEq/L, but treatment was initiated before the development of serious symptoms could develop.

We treated a case wherein SIADH developed after pancreatoduodenectomy for pancreatic head cancer. This is a valuable case in which SIADH caused by surgical invasion was discovered early after major gastrointestinal surgery, and treatment was immediately started. We performed an operation that involved reconstruction of the digestive tract and this detection of SIADH was difficult, as it was based only on the digestive symptoms. However, it is important that SIADH be diagnosed in the early stage and sodium supplementation should be initiated to prevent irreversible damage.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

N.K. and I.O. made a substantial contribution to the concept and design of the study and to data acquisition and interpretation. M.I., K.T., and T.T. were involved in drafting the manuscript and critical revision of the intellectual content. N.K. approved the final version of the manuscript submitted for publication. All authors have read and approved the manuscript.

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